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Chapter

The Genetic Aspects of Behçet's Disease: Role of Cytokine Genes Polymorphisms

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Abstract

Behçet's disease (BD) is a complex, multisystemic inflammatory disorder characterized by recurrent oral aphthous ulcers, ocular symptoms, skin lesions, and genital ulcerations. The etiology of BD is not yet clear though various factors including environmental, genetic and immunological ones have been implicated. Genetic predisposition is a major factor in disease susceptibility and multiple host genetic factors have been suggested to be involved in the development of BD. In addition to the positive association of HLAB*51, recent studies report additional independent associations in the non HLA loci. Single nucleotide polymorphisms (SNPs) in various genes including cytokines have been implicated in susceptibility to BD. However, the results are inconsistent and variation are found in several ethnic populations. Therefore, further genetic studies on BD patients of different ethnicity and genes associated with immunity are expected to elucidate BD pathogenesis and will contribute to the development of more targeted therapies and biomarkers.

Keywords: Behçet's disease, genetics, cytokines, TNF, interleukin, polymorphism

1. Introduction

Behçet's disease (BD; MIM 109650) is a multisystemic inflammatory disorder characterized by recurrent oral aphthous ulcers, ocular symptoms, skin lesions, and genital ulcerations. BD has many features in common with systemic vasculitis. The prevalence of BD varies, it is more prevalent in the Far East, the Mediterranean and the Middle Eastern countries along the ancient Silk Road [1–3]. The highest prevalence has been reported in Turkey (80–420 cases per 100,000) followed by Israel (146.4), China (110), Iran (80), Korea (30.2), Japan (22), Saudi Arabia (20), Iraq (17), Morocco (15), and Egypt (7.5) cases per 100,000 [1, 3, 4].

Clinical and immunological understandings of the disease suggest that BD is a cornerstone between autoimmune and inflammatory disease [5]. Due to effectiveness of immunosuppressives [6] and involvement of human heat-shock protein 60 (HSP60) [7], it is considered as an autoimmune disease. While on the basis of lack of antigen-specific T-cells or significant high-titer auto-antibodies, insignificant involvement of histocompatibility complex (MHC) class I molecules together with unprovoked recurrent inflammation episodes mainly caused by neutrophils [8], the association of the M694V MEFV mutation with its susceptibility and the therapeutic effectiveness of colchicine, BD is classified as an auto-inflammatory disease [4].

Although it is thought that common environmental factors such as infections or exposures to toxins or to specific immunogens contribute to BD, development of disease is believed to occur only in genetically predisposed hosts. BD is a complex disease and different patients experience different symptoms. The etiology of BD is very complex and it is thought that environmental factors, genetic predisposition and immune dysregulation are involved in the pathogenesis of BD [9–14]. The wide range of disease prevalence observed among different geographic locales is likely a result of differences in both environment and genetics. The aim of this study is to highlight the genetic aspect of BD with emphasis on the role of cytokine genes polymorphisms in the susceptibility/etiopathogenesis of BD.

2. Genetic aspect of Behçet's disease

Genetic predisposition is a major factor in disease susceptibility and multiple host genetic factors have been suggested to be involved in the development of BD. The association of HLAB*51 with BD susceptibility has been confirmed in several populations since it was discovered more than four decades ago however, recent studies indicate association in the major histocompatibility complex class I region and several non HLA loci also. Class I alleles, HLA-A*26, -B*15, -B*27, and -B*57, have been reported as independent risk factors for Behçet's disease while HLA- A*03 and -B*49 are protective for it [15].

The candidate gene approach has been useful in identifying susceptibility and severity genes in BD. Single nucleotide polymorphisms (SNPs) in various genes (IL-10, TNF-α, TNF-β, STAT4, IL23R, CD40, CCR1/CCR3, STAT3, MCP-1, TGFBR3, FCRL3, SUMO4, UBAC2) have been implicated in susceptibility to BD. However, the results are inconsistent and variation are found in several ethnic populations. Genome-wide association studies have also identified associations with IL23R–IL12RB2, IL10, STAT4, CCR1-CCR3, KLRC4, ERAP1, TNFAIP3, and FUT2 loci [15]. Moreover rare mutations in IL23R, TLR4, NOD2, and MEFVr genes have been found to be linked with BD pathogenesis by targeted next-generation sequencing.

The variations in the mRNA expression/gene function indicate the role of the risk alleles in the pathogenesis of disease. Several susceptibility genes, which may regulate the immune reaction, have been found to be associated with BD. However, the precise mechanism of these genes in the development of BD is currently unknown [10, 11, 16]. The genes identified are involved in both innate and adaptive immunity and support the idea that polarization in Th1/Th17 pathway plays a critical role in BD pathogenesis. Commonalities of susceptibility genes with other immune-related diseases/inflammatory disorders shows shared features of immune related diseases with BD. The interaction between genetic factors and environmental factors has also been suggested in several recent studies.

Cytokines are believed to mediate inflammation in BD [17, 18]. Various studies have found increased levels of tumor necrosis factor (TNF)-α and decreased levels of interleukin (IL)-10 in the serum and active lesions of BD patients and suggested that these cytokines play a significant role in the immune response, pathogenesis and activity in BD [12, 19–24].

Cytokines play critical roles in the pathogenesis of BD, since they mediate many of the effector and regulatory functions of immune and inflammatory responses [14, 17]. Genetic polymorphisms in several cytokine genes have been described and demonstrated to influence gene transcription, leading to inter individual variations in cytokine production. It has been suggested that genetic polymorphisms that regulate the production of certain cytokines are important determinants of susceptibility to BD and its some of the clinical and laboratory features [14, 25, 26]. BD has

been considered to be a typical Th1-mediated inflammatory disease, characterized by elevated levels of Th1 cytokines such as IFN-γ, IL-2, and TNF-α. Recently it has been reported that Th1- and Th17-related cytokines and signaling molecules participated in BD pathogenesis [27, 28].

A number of studies reported that the levels of T helper Type 1 cytokines are increased in sera of the patients with BD. Some studies have shown that the maximal capacity of cytokine production varies among individuals and correlate with single nucleotide polymorphism in various cytokine genes [29–32]. However the results of the association of cytokines genes polymorphism with susceptibility and pathogenesis of BD are inconsistent and further studies involving different ethnic populations have been suggested [14].

3. Tumor necrosis factor (TNF)-α polymorphisms

Besides HLA-B51 molecules, SNPs in TNF genes have been implicated in susceptibility to BD [14, 33–37]. TNF-α is a pro-inflammatory cytokine and involved in regulation of the immune response. It is encoded in the Class III region of the HLA complex adjacent to HLA-B. TNF-α mediates the activation of macrophages and apoptosis and it is involved in recurrent inflammatory episodes in BD patients [23, 38]. Many studies have suggested it as both positional and functional candidate gene in the onset and progression of BD [14, 33–35, 39].

Promoter polymorphism of TNF-α (−308G/A) and intronic polymorphism TNF-β (252A/G) have been associated with variations in the level of circulating TNF-α [40]. TNF-α (−308G/A) polymorphism (rs1800629) results into a less common allele-A (allele 2) which leads to increased TNF-α production in vitro [41] and higher rate of TNF-α transcription than wild type allele-G (allele 1). Allele-A produces 6–7 fold higher levels of TNF-α transcription [42–44]. TNF-α production and expression is regulated by single nucleotide polymorphisms (SNPs) in TNF-α gene [25, 42]. Several SNPs in TNF-α gene have been associated BD in different ethnic groups [14, 36, 45–47]. The outcome of various studies on association between BD and SNPs of TNF-α in different ethnic groups are summarized in **Tables 1**–**6**.

3.1 TNF-α (−308 G/A) polymorphism

A number of studies has determined the relationship between the -308A/G polymorphism and BD with inconsistent results (**Table 1**). The genotype GA and allele-A are associated with susceptibility of BD in Saudis [14] while genotype GG and allele G are associated with its susceptibility in Korean patients [33]. On the other hand no association is found in Caucasoid [39], Iranian [48], Iranian (Azeri Turkish) [54], Korean [49, 50] Lebanese [51], Tunisian [46], Turkish [38, 45, 52, 53] and Moroccan [47].

Two independent meta-analysis have revealed an association between −308A and BD risk in the overall [34, 35] however, stratification by ethnicity indicates that the −308A allele is significantly associated with BD risk in the Asian population [35].

3.2 TNF-α (−238 A/G) polymorphism

The TNF-238A/G polymorphism has been studied in BD patients from different ethical populations and several reports are available on the association between the TNF−238A/G polymorphism and BD risk with contrast results. Genotype AA is found to be associated with BD in Turkish population [55] whereas genotype GG is associated with BD in Iranian patients [48]. Other individual studies on German

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Saudi	61/211	GA/A	Susceptible	[14]
Korean	254/344	GG/G	Susceptible	[33]
Korean	94/94	GA polymorphism	No association	[49]
Korean	115/114	GA polymorphism	No association	[50]
Turkish	99/96	GA polymorphism	No association	[52]
Turkish	107/102	GA polymorphism	No association	[38]
Turkish	97/127	GA polymorphism	No association	[53]
Turkish	102/102	GA polymorphism	No association	[45]
Lebanese	48/90	GA polymorphism	No association	[51]
Iranian	147/137	GA polymorphism	No association	[48]
Iranian (Azeri Turkish)	53/79	GA polymorphism	No association	[54]
Moroccan	120/112	GA polymorphism	No association	[47]
Tunisian	89/157	GA polymorphism	No association	[46]
Caucasoid	133/354	GA polymorphism	No association	[39]
Meta-analysis	–	GA polymorphism	No association	[36]
Meta-analysis	1372/1754	GA polymorphism	Susceptible	[34]
Asian*	1232/1397	A-allele	Susceptible	[35]

**Meta-analysis.*

Table 1.
Association of TNF-α-308 polymorphism with BD susceptibility.

[56], Iranian (Azeri Turkish) [57], Korean [33, 50], Lebanese [51], Moroccan [47] and Turkish [38, 56] BD patients show no association of TNF−238A/G polymorphism with susceptibility of BD (**Table 2**). However two meta-analysis indicates that allele-A is associated with BD susceptibility [35, 36]. In the subgroup analysis by ethnicity, Zhang et al. [35] suggests that the BD cases has a significant higher frequency of A in the Caucasian than that in the controls.

3.3 TNF-α (−1031 C/T) polymorphism

There is a strong evidence indicating the role of TNF-α (−1031 C/T) Polymorphism with BD susceptibility. A number of studies examined the association of TNF-α −1031C/T with BD in different populations. Results indicate, a significant association between the TNF-α −1031C/T polymorphism and BD susceptibility in

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Turkish	107/102	A/G polymorphism	No association	[38]
Turkish	80/105	AA	Susceptible	[55]
Turkish	30/20	A/G polymorphism	No association	[56]
Korean	254/344	A/G polymorphism	No association	[33]
Korean	115/114	A/G polymorphism	No association	[50]
German	92/51	A/G polymorphism	No association	[56]
Lebanese	48/90	A/G polymorphism	No association	[51]
Moroccan	120/112	A/G polymorphism	No association	[47]
Iranian	150/140	GG	Susceptible	[48]
Iranian (Azeri Turkish)	64/101	A/G polymorphism	No association	[57]
Meta-analysis	–	A-allele	Susceptible	[36]
Caucasian*	842/938	A-allele	Susceptible	[35]

**Meta-analysis.*

Table 2.
Association of TNF-α –238 polymorphism with BD susceptibility.

Turkish [29, 58], Iranian (Azeri Turkish) [54], Korean [33], and Tunisian patients [46] (**Table 3**). Touma et al. [36] in a meta-analysis, identified a significant associations between the −1031C/T polymorphisms and BD risk. Stratifying by ethnicity, in another meta-analysis a significant association in the Caucasian population is noticed [35]. Radouane et al. [47] suggested that TNF-1031C constitutes a susceptibility allele for BD in Moroccan, especially with genital ulcers.

In contrast, Chang et al. [50] discovered no significant difference in the allele frequency of TNF-α −1031C/T between patients with BD and controls in a Korean population. There was no significant association of this polymorphism in Lebanese BD patients also [51]. Moreover the analysis of the influences this polymorphism on various clinical manifestations of BD showed that TNF-α −1031C is not related to the presence of clinical features, such as oral and genital ulceration and uveitis.

3.4 TNF-α (−857 T/C) polymorphism

A number of studies has been focused on the association between the TNF-α-857T/C polymorphism and BD risk [**Table 4**]. Two independent studies indicate an association of TNF-α-857T/C polymorphism with BD susceptibility in Korean and Iranian (Azeri Turkish) Cohort [33, 57]. Other studies performed on Korean, Lebanese, and Moroccan BD patients show no significant association of this polymorphism and BD susceptibility [47, 50, 51]. However a meta-analysis suggested that T-allele of TNF-α-857T/C polymorphism is associated with BD susceptibility [36]. Later on another meta-analysis also indicated that this association is a significant risk factor in Asian population [35].

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Turkish	99/103	C/T polymorphism	Susceptible	[29]
Turkish	82/77	CC	Susceptible	[58]
Iranian (Azeri Turkish)	53/79	C-allele	Susceptible	[54]
Korean	254/344	C/T polymorphism	Susceptible	[33]
Korean	115/114	C/T polymorphism	No association	[50]
Tunisian	89/157	C-allele	Susceptible	[46]
Lebanese	48/90	C/T polymorphism	No association	[51]
Caucasoid (UK)	133/354	C/T polymorphism	Susceptible	[39]
Moroccan	120/112	C-allele	Susceptible	[47]
Meta-analysis		C- allele	Susceptible	[36]
Caucasian*	738/964	C- allele	Susceptible	[35]

Meta-analysis.

Table 3.
Association of TNF-α –1031 polymorphism with BD susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Korean	254/344	C-allele	Susceptible	[33]
Korean	115/114	T/C polymorphism	No association	[50]
Lebanese	48/90	T/C polymorphism	No association	[51]
Moroccan	120/112	T/C polymorphism	No association	[47]
Iranian (Azeri Turkish)	64/101	C-allele	Susceptible	[57]
Meta-analysis		T-allele	Susceptible	[36]
Asian*	533/660	T/-allele	Susceptible	[35]

Meta-analysis.

Table 4.
Association of TNF-α –857 polymorphism and BD in various populations.

3.5 TNF-α (−863 A/C) polymorphism

TNF-863A/C polymorphisms has been studied in Korean, Moroccan and Lebanese BD patients. Results of these studies indicated that there is no significant association of polymorphism with BD susceptibility (**Table 5**) [47, 50, 51] though one study suggested an association in Korean patients [33]. However two independent meta-analysis also did not find any significant role of this polymorphism in BD susceptibility [35, 36].

3.6 TNF-α (−376 A/G) polymorphism

Three reports are available on −376A/G polymorphism in BD, two studies were performed in Turkish while the third one in Moroccan patients. These studies identified no significant association with BD risk (**Table 6**). The results of the meta-analysis

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Korean	254/344	A/C polymorphism	Susceptible	[33]
Korean	115/114	A/C polymorphism	No association	[50]
Moroccan	120/112	A/C polymorphism	No association	[47]
Lebanese	48/90	A/C polymorphism	No association	[51]
Meta-analysis	–	A/C polymorphism	No association	[36]
Asian*	486/560	A/C polymorphism	No association	[35]

**Meta-analysis.*

Table 5.
Association of TNF-α–863 polymorphism with BD in various populations.

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Turkish	99/96	A/G polymorphism	No association	[52]
Turkish	107/102	A/G polymorphism	No association	[38]
Moroccan	120/112	A/G polymorphism	No association	[47]

Table 6.
Association of TNF-α–376 polymorphism with BD susceptibility.

by Zhang et al. [35] also showed that the TNF-376A/G polymorphism is not associated with BD susceptibility and this polymorphism does not appear to have a significant association with overall BD risk.

4. TNF-β (–252A/G) polymorphism

TNF-β has been reported to contribute to the susceptibility of some inflammatory and autoimmune diseases [58–62]. Gamma delta T cells of BD patients produce higher levels of TNF-β than those of healthy controls [63, 64]. A polymorphism in the intron 1 of TNF-β has been associated with higher TNF-α and TNF-β production. TNF-β (+252A/G) polymorphism (rs909253) contains a Guanine (G) on one allele and an adenine (A) on the alternate allele. TNF-β +252G allele is defined as mutant allele and known as TNF-β*1 (allele-1). This mutant allele-1 is associated with increased levels of TNF-α and TNF-β [65, 66].

To the best of our knowledge five studies have been focused on TNF-β (+252A/G) polymorphism and BD (**Table 7**). The results of three studies in Saudi, Korean and Tunisian BD patients indicated that TNF-β (+252A/G) polymorphism has no significant association with BD susceptibility. However one report from

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Saudi	61/211	AG polymorphism	No association	[14]
Tunisian	89/157	AG polymorphism	No association	[46]
Korean	94/94	AG polymorphism	No association	[49]
Middle eastern	102/115	A-allele	Susceptible	[67]
Japanese	79/75	A-allele	Susceptible	[68]

Table 7.
Association of TNF-β–252 polymorphism with BD susceptibility.

Palestinian and Jordanian populations indicates that the frequency TNF-β +252 A allele (allele-2) is increased in BD cases compared to controls [67]. On the basis of strong linkage disequilibrium found between HLA-B*51 and allele-A of TNF-β (+252A/G) polymorphism it has also been suggested that that both the alleles contribute to BD risk and their co-expression may cause severe eye pathogenicity leading to blindness [67]. Another report by Mizuki et al. [68] shows that the frequency of homozygous genotype (GG) of TNF-β (+252A/G) is significantly decreased in Japanese ocular BD patients than controls.

5. Interleukin (IL) gene polymorphisms

Interleukins are cytokines that mediate communication between cells. Interleukins regulate cell growth, differentiation, and motility. They are particularly important in stimulating immune response, such as inflammation. ILs (IL-1 to IL-38) function and play significant role in various diseases and their expression/production is influenced by the polymorphisms and mutations in their encoding genes [69].

5.1 IL-10 gene polymorphism

IL10 gene encodes IL-10 cytokine which suppresses the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-12, TNF, and interferon gamma (IFN-γ), and inhibits the costimulatory activity of macrophages for T cell and NK cell activation [70]. IL-10 production may be regulated at the transcriptional level and several single nucleotide polymorphisms (SNPs) at the promoter region of IL-10 gene have been shown to be associated with changes in the expression levels of IL-10 [25, 42].

Numerous recent studies have demonstrated an association between BD and SNPs of IL10. Three polymorphisms -1082 A/G (rs1800896), -819 T/C (rs1800871) and -592 A/C (rs1800872) in the promoter region of the IL-10 gene are correlated to the expression level of IL-10. There are inconsistent reports on the association of IL-10-1082 A/G, -819 T/C and -592 A/C polymorphisms and BD (**Tables 8–10**). Two recent studies suggested significant association of genotype GG of IL-10-1082 A/G with BD susceptibility in Saudis [14] and Egyptian [71]. Earlier Wallace et al. [72] showed weak association of genotype AA with BD in UK and middle-eastern cohort. Moreover a meta-analysis also shows that there is a significant association of IL-10-1082 A/G polymorphism with BD susceptibility [34]. While there is no significant association of this polymorphism in Turkish and Iranian BD patients (**Table 8**) [28, 45, 53].

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Saudi	61/200	GG	Susceptible	[14]
Egyptian	87/97	GG	Susceptible	[71]
UK+ME	178/295	AA	Weekly associated	[72]
Turkish	97/127	GA polymorphism	No association	[53]
Turkish	102/102	GA polymorphism	No association	[45]
Iranian	150/140	GA polymorphism	No association	[28]
Meta-analysis	199/229	GG+GA	Susceptible	[34]

Table 8.
Association of IL-10-1082 polymorphism with BD susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Saudi	61/200	TT	Susceptible	[14]
Chinese	407/679	CT polymorphism	Susceptible	[74]
Chinese Han	718/1753	T-allele	Susceptible	[75]
Algerian	51/96	T-allele	Susceptible	[73]
British	178/295	T-allele	Susceptible	[72]
Turkish	102/102	CT polymorphism	No association	[45]
Turkish	97/127	CT polymorphism	No association	[53]
Turkish	1215/1279	CT polymorphism	No association	[11]
Japanese	611/737	CT polymorphism	No association	[11]
Korean	119/140	CT polymorphism	No association	[11]
Iranian	150/140	CT polymorphism	No association	[28]
Overall mixed	1945/2156	CT polymorphism	Susceptible	[11]
Meta-analysis	2472/2820	CT polymorphism	Susceptible	[34]

Table 9.
Association of IL-10-819 polymorphism with BD susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Saudi	61/200	AA	Susceptible	[14]
Algerian	51/96	A-allele	Susceptible	[73]
Iranian	150/140	CA polymorphism	No association	[28]
Iranian (Azeri Turkish)	47/58	A-Allele	Susceptible	[76]
Chinese Han	718/1753	A-Allele	Susceptible	[75]
Spanish	304/313	A-Allele	Susceptible	[77]
Turkish	102/102	CA polymorphism	No association	[45]
Turkish	97/127	CA polymorphism	No association	[53]
Turkish	1215/1279	CA polymorphism	No association	[11]
Japanese	611/737	CA polymorphism	No association	[11]
Korean	119/140	CA polymorphism	No association	[11]
Overall mixed	1945/2156	CA polymorphism	Susceptible	[11]
Meta-analysis	2294/2525	CA polymorphism	Susceptible	[34]

Table 10.
Association of IL-10-592 polymorphism with BD susceptibility.

IL-10-819 T/C polymorphism has been studied in different populations (**Table 9**). Reports indicate that IL-10-819 T/C polymorphism is associated with susceptibility of BD in Algerians [73], British [72], Chinese [74, 75] and Saudi patients [14]. While it is not significantly associated with BD in Turkish [11, 45, 53], Iranian [28], Japanese and Korean patients [11]. However two independent meta-analysis showed that IL-10-819 T/C polymorphism is associated with BD [11, 34]. In a meta-analysis containing of 2472 cases and 2820 controls, Liang et al. [34] suggested that IL-10-819 T/C polymorphism is associated with BD susceptibility.

Available literature shows that 11 studies focused on relationship of IL-10-592 A/C polymorphism and BD risk (**Table 10**). A significant association of this polymorphism has been reported in five studies from different ethnicity namely Algerian [73], Iranian (Azeri Turkish) [76], Chinese Han [75], Saudi [14] and Spanish BD patients [77]. In our study with Saudi patients we found that −592 AA genotypes of IL-10 is significantly associated with susceptibility risk of BD in Saudi patients [14].

On the other hand three studies on Turkish [11, 45, 53], one each on Iranian [28], Japanese and Korean BD patients [11] show no significant association of this polymorphism with BD susceptibility. A meta-analysis containing 2294 patients and 2525 controls suggested that IL-10-592 A/C polymorphism is associated with BD susceptibility [34].

Two independent GWA studies of Turkish and Japanese populations show that IL-10 is among the first two BD susceptibility loci outside the MHC with genome-wide significance [11, 16]. Intronic polymorphism (rs1518111) is associated with BD susceptibility in the Turkish population [16] while promoter polymorphisms in IL-10 gene (rs1800871 and rs1800872) are associated with BD in Japanese [11]. The variant rs1518111 has been replicated in BD patients of British, Greek, Korean and Middle Eastern ethnicity and rs1800872 replicated in Turkish and Korean samples [11, 16]. Recently Wu et al. [74] reported the replication of rs1518111 and rs1800871 variants in BD patients from Han Chinese population. The SNP rs1518111 has also been replicated in in the Iranian population showing association with BD [78]. The data from HapMap Project indicate that these three polymorphisms are in strong linkage disequilibrium in populations from both European and Asian ancestries. The decrease in risk allele A of rs1518111 is associated with decreased IL10 expression in monocytes by 35% compared with the non-risk allele G in Turkish patients with BD.

The homozygous genotype AA of rs1518111 is associated with decrease in IL-10 protein in monocytes and found to be stimulated with Toll-like-receptor ligands, such as lipopolysaccharide or the lipoprotein Pam3Cys and muramyl dipeptide [16]. Talat et al. [71] reported that IL-10 serum levels are lower in BD patients than in controls. Baris et al. [79] suggested that IL-10 polymorphisms can be statistically associated with the disease symptoms and used as prognostic factors.

5.2 IL-1 gene polymorphism

Several cytokine genes may play crucial roles in host susceptibility to Behçet's disease (BD), since the cytokine production capacity varies among individuals and depends on the cytokine gene polymorphisms. Interleukin-1 (IL-1) and the IL-1 receptor (IL-1R) family plays an important role in the pathogenesis of inflammatory diseases. The association of the IL-1 cluster gene polymorphisms with the development of BD has been investigated in several studies.

5.2.1 IL-1α −889C/T polymorphism

Six reports are available on IL-1α -889C/T polymorphism and Behçet's disease (**Table 11**). Out these five studies were performed on Turkish patients [55, 58, 80–82] while one on Iranian BD patients [48]. There was no association of this gene polymorphism and the susceptibility of BD except one study which showed CC genotype to be associated with BD susceptibility in Turkish patients [55].

5.2.2 IL-1β −511C/T polymorphism

Four studies are found which focused to assess the importance of IL-1β −511C/T polymorphism for BD susceptibility (**Table 11**). The comparisons of allele and

Population	Case/controls	Polymorphism	Association	Reference
Turkish	132/106	IL-1α-889C/T	No association	[80]
Turkish	72/163	IL-1α-889C/T	No association	[81]
Turkish	80/105	IL-1α-889C/T	CC associated	[55]
Turkish	57/57	IL-1α-889C/T	No association	[58]
Turkish	97/77	IL-1α-889C/T	No association	[82]
Iranian	150/140	IL-1α-889C/T	No association	[48]
Turkish	132/106	IL-1β-511C/T	No association	[80]
Turkish	80/105	IL-1β-511C/T	CC associated	[55]
Turkish	57/57	IL-1β-511C/T	No association	[58]
Turkish	97/77	IL-1β-511C/T	No association	[82]
Turkish	57/57	IL-1β-3962C/T	No association	[58]
Turkish	80/105	IL-1β-3962C/T	CC associated	[55]
Turkish	97/77	IL-1β-3962C/T	No association	[82]
Iranian	150/140	IL-1β-3962C/T	No association	[48]

Table 11.
Association of IL-1 polymorphisms with BD susceptibility.

genotype failed to detect any statistical association under the random effect model in three studies [58, 80, 82] however one study reported that CC genotype of IL-1β −511C/T polymorphism is associated with BD susceptibility in Turkish patients [55].

5.2.3 IL-1β −3962 C/A polymorphism

Some workers have studied IL-1 β −3962 C/A polymorphism and assessed the effect of the IL-1β −3962C/A polymorphism in the occurrence of BD in Turkish and Iranian patients (**Table 11**). They did not find any significant association between IL-1β −3962 C/A polymorphism with BD between allele and genotype frequencies in Turkish and Iranian BD patients [48, 58, 82] however one study indicates association of IL-1 β −3962 C/A polymorphism with BD in Turkish patients [55].

Ozçimen et al. [82] studied IL-1 cluster gene polymorphisms in Turkish patients with Behçet's disease and suggested that polymorphisms in IL-1β gene may affect host susceptibility to BD. The IL-1β production in the active period has been found to be greater than in the remission period of BD. IL-1β production is considered to be related to posterior segment type attacks of Behçet's disease [83].

Baris et al. [79] observed no significant differences between the groups with respect to the IL-1Ra, IL-1β, IL-2, IL-6 and the IL-10 gene polymorphism distributions and suggested that the IL-1RN2 gene polymorphism is correlated with the presence of articular involvement and the IL-1β gene polymorphism with the presence of an ocular lesion. On the basis of the correlations between the articular involvement and IL-1RN, the ocular involvement and the IL-1β, gene polymorphisms, it has been suggested that these polymorphisms could be statistically associated with the disease symptoms and may be used as prognostic factors [79].

6. Interleukin (IL)-6

IL-6 pleitropic cytokine is involved in immune and inflammatory responses. Various polymorphisms in IL-6 gene have been associated with chronic inflammatory

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Tunisian	43/43	G/C polymorphism	No association	[20]
Egyptian	87/97	G/C polymorphism	No association	[71]
Iranian	150/140	GG	Protective	[48]
Turkish/German	121/70	G/C polymorphism	No association	[56]
Turkish	97/127	G/C polymorphism	No association	[53]
Korean	89/123	G/C polymorphism	No association	[90]
Meta-analysis	2065/1159	G/C polymorphism	Decrease the risk	[91]

Table 12.
Association of IL-6 (174G/C) polymorphism with BD susceptibility.

and autoimmune disorders [84–88]. Higher levels of IL-6 and increased expression of IL-6 mRNA have been reported in subjects with active BD [20, 89, 90]. A few studies have focused on the polymorphism of IL-6 −174 G/C in BD patients (**Table 12**). The polymorphism of IL6 −174 G/C does not modulate clinical expression of BD. The single nucleotide polymorphism of the IL-6 does not appear to be associated with BD susceptibility in Egyptian [71], Korean [90], Tunisian [20], Turkish and German patients [53, 56]. The GG genotype of IL-6 −174 G/C polymorphism is protective in Iranian population [48]. It is believed that the scarcity of studies of polymorphism of IL-6 in BD is related to the fact that IL-6 is a pro-inflammatory cytokine of Th2, whereas BD is a Th1 disease. Recently a meta-analysis suggested that IL-6-174 G/C polymorphism decreases the risk of BD [91].

7. IL23R-IL12RB2 polymorphisms

The IL23R–IL12RB2 polymorphisms in Behçet's disease have been subject of several studies in various ethnic populations (**Table 13**). The IL23R–IL12RB2 locus is one of the few loci with genome-wide significance. The SNP rs1495965, located in the intergenic region between IL23R and IL12RB2 is associated with BD in Japanese [11]. Another polymorphism (rs924080) in the intergenic region between IL23R and IL12RB2 has been associated with BD in Turkish patients [16]. However, these association are not replicated in Korean, Middle Eastern Arab, Greek, and British subjects possibly due to small sample size [16].

The rs924080 has been replicated in the Iranian population and major allele is associated with BD [78]. Other polymorphisms rs7539328, rs12119179, rs1495965 have also been associated with BD susceptibility in Iranian patients [92]. Moreover minor allele of IL23R polymorphisms, Arg381Gln in the Turkish population and Gly149Arg in the Japanese population are associated with protection from BD as these variants reduce its ability to respond to IL-23 stimulation [99]. Disease–associated, intergenic non-coding variants (major alleles) are associated with increased expression of IL23R compared with the disease-protective minor alleles [99].

The IL-23 receptor is expressed on the surface of Th17 cells and macrophages. It is encoded by *IL23R* gene. IL-23 is composed of p19 and p40 subunits which is shared with IL-12. IL-23, being a proinflammatory cytokine promotes Th17 cell

Population	Case/controls	Polymorphism	Association	Reference
Iranian	973/637	rs10489629 rs1343151 rs1495965	Susceptible	[78]
Iranian	552/417	rs7539328, rs12119179, rs1495965,	Susceptible	[92]
Korean	369/2000	rs1495965 rs1495966 rs4655535	Susceptible	[93]
Chinese Han	407/421	rs924080 rs11209032	Susceptible	[94]
Chinese Han	1206/2475	rs3024490 rs12141431	Susceptible	[95]
Chinese Han	806/1600	rs3212227	Susceptible	[96]
Chinese Han	27/32	rs17375018	Susceptible	[97]
Algerian	51/96	rs12119179 rs11209032 rs924080	decrease risk	[73]
Egyptian		rs17375018	Susceptible	[13]
Turkish	123/168	rs17375018	Susceptible	[98]
Japanese	612/740	rs1495965	Susceptible	[11]
Turkish	2430/2660	rs924080	Susceptible	[16]

Table 13.
Association of IL23R-IL12RB2 polymorphisms with BD susceptibility.

development and induces the production of IL-1, IL-6, IL-17 and TNF [100]. Th17 cells by producing IL-17 play a significant role in inflammation and autoimmune diseases. Steinman [101] suggested that the disease-associated alleles increase IL-23 receptor expression or signaling compared with the disease-protective alleles. Thus it is evident that the disease-associated variants increase the BD susceptibility by influencing IL23R, however an alternative or additional role to influence expression of the other nearby gene, like IL12RB2, cannot be excluded. IL-12 receptor beta2, a subunit of IL-12 receptor is encoded by *IL12RB2* gene. *IL12RB2* is responsible for high-affinity IL-12 binding and IL-12 dependent signaling, and plays an important role in Th1 cell differentiation. IL-12 has been suggested to be involved in Th1 responses, T cell and NK cell cytotoxicity, and IFN-γ production by T cells and NK cells [102]. As there is no data available on quantitative trait loci for these non-coding variants influencing IL12RB2 or IL23R expression, there is a possibility that their effects are expressed only in a specific cell type or under certain conditions as suggested by Takeuchi et al [15].

Yu et al. [95] performed genome wide association study on 1206 patients with BD and 2475 healthy controls and confirmed the association of IL-10 819 C/T and IL23R IL12RB2/rs924080 with BD. They (loc. cit.) also identified two susceptibility single nucleotide polymorphisms in IL10 and IL23R-IL12RB2 (rs3024490 and rs12141431) with BD in Han Chinese.

8. IL12A polymorphisms

IL12A encodes IL-12p35, a subunit of the heterodimer of IL-12, is known to play a critical role in polarization of the Th1 pathway through differentiation from

naïve CD4+ T cells. A variant rs1780546, located in the intergenic region near IL12A has been associated with BD in a Turkish cohort however the association did not achieve genome-wide significance as it is not polymorphic in the Japanese cohort [99]. Recently, Kappen et al. [103] reported an association of rs1780546 with BD susceptibility and showed genome-wide association after meta-analysis with previous Turkish GWAS data. This GWAS was based on 336 cases and 5843 controls in cohorts of mixed ethnicity using linear mixed models to correct for ancestry differences and family structure and/or cryptic relationships. However no report is available on functional aspect of rs1780546 [102].

9. IL-33 gene polymorphism

Members of the IL-1 family play a pivotal role in the inflammatory responses [104]. IL-33 belongs to IL-1 superfamily. Some studies have implicated the IL-33 ligand for the ST2 receptor in the pathogenesis of BD [105–107]. IL-33 is encoded by *IL-33* gene and expressed in epithelial, endothelial, inflammatory and central nervous system cells. IL-33 can function both as a cytokine and as a nuclear factor regulating gene transcription due to the fact that its expression increases in pro-inflammatory conditions. Cells of the affected area play a significant role in the pathogenesis of BD by recruiting, activating and promoting survival of inflammatory cells. Therefore the use of immunosuppressant like azathioprine, cyclosporine, corticosteroids or anti-TNF-α monoclonal antibodies (mAb) which interferes the cytokine network is the basis of BD treatment strategies [6, 20, 108].

The TT variants of rs7044343 and rs11792633 polymorphisms in IL-33 gene are very rare, and the T allele frequencies of these polymorphisms has been reported to be lower in the BD group compared to the controls. The rs7044343 and rs11792633 variants of IL-33 gene are associated with the decreased risk of BD in Turkish cohort. It has been suggested that IL-33 acts a protective role on the pathogenesis of BD [109].

10. Interferon-γ (IFN-γ)

IFN-γ is antiviral, antitumor and immunomodulatory cytokine. It has a critical role in modulating the IL-4, IL-10 and IL-12 cytokine network pathway. It is also considered as a pro-inflammatory cytokine because of its effects on TNF activity. It has been reported that the frequencies of IFN-γ +874A allele and A/A genotype are higher in BD patients than in healthy controls, and individuals with this genotype are more susceptible to the disease [55]. However later studies on Turkish and Iranian patients failed to find any significant association of IFN-γ +874 A/T polymorphism with BD susceptibility (**Table 14**) [28, 53].

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Turkish	80/105	AA/A	Susceptible	[55]
Turkish	97/127	A/T polymorphism	No association	[53]
Iranian	150/140	A/T polymorphism	No association	[28]

Table 14.
Association of IFN-γ (+874A/T) polymorphism with BD susceptibility.

11. Transforming growth factor-β1 gene polymorphism

Transforming growth factor-β1 (TGF-β1) is an effective immunosuppressive cytokine. It is produced in response to tissue injury by activated macrophages. TGF-β1 is responsible for inhibition of macrophage activation and modulation of T cell function [110, 111]. It is also involved in tissue fibrosis by increasing the synthesis of extracellular matrix components [112]. The frequency of TGF-β1 codon 10–25 T/C-G/C genotype in Turkish BD patients has been reported to be higher than those of healthy controls [53] while GG genotype has been reported to be susceptible to BD in Iranian cohort (**Table 15**) [28].

Recent studies have focused on the functional relevance of the various genes associated with susceptibility of BD and possible interaction between the genes located within and outside the MHC region [14, 24, 113, 114]. The functional relevance of allele A and genotype GA of TNF-α (308G/A) and association with BD has been indicated in various studies [24, 114]. The increased frequency of allele-A in BD patients is linked with higher levels of TNF-α reported in active BD patients as compared to controls [24, 114].

The pro-inflammatory cytokines induce inflammation and the severity of the inflammatory responses is influenced by the levels of cytokines. The activated macrophages produce higher levels of cytokines affecting not only the severity of the local inflammatory responses but also exert systemic effects. The over-expression of these cytokines is considered to be responsible for the pathogenesis of recurrent BD [33]. TNF-α, a pro-inflammatory cytokine has been suggested to be responsible for the pathogenesis of BD by activating T-cells and neutrophils [115].

On the other hand increased frequency of low producer 1082GG genotype of IL-10 (an anti-inflammatory cytokine) in BD patients may not suppress the TNF-α- activity and resulting inflammatory responses, as IL-10 is known to limit the secretion of pro-inflammatory cytokines, such as TNF-*α* and IL-12 [70]. Moreover the deficiency of IL-10 and resulting prolonged activation of mononuclear cells may lead to an augmented efflux of inflammatory cytokines and further aggravate the severity of BD as IL-10 is a multi-functional cytokine with role in diverse areas of the human immune system [116].

The information regarding the association of various gene polymorphisms will have prognostic value for future clinical observations. Especially the data of TNF-α (−308) polymorphism will provide guideline in anti-TNF-α therapy as patients with GG genotype are better responders to anti-TNF-α treatment than those with AA or GA [117, 118]. However, such genetic associations with BD susceptibility need further validation and investigation in more patients with BD from various ethnic populations, as they may have implications for the development of novel therapies as suggested by Xavier *et al* [78].

Population	Case/controls	Genotype/allele	Association	Reference
Turkish	97/127	T/C-G/C	Susceptible	[53]
Iranian	150/140	CC	Susceptible	[28]

Table 15.
Association of TGF-β1 (509 C/T) polymorphism with BD susceptibility.

12. Conclusion

In spite of recent advances in genetics and immunology leading to a better understanding of the immunopathogenesis, the etiology of BD is still unclear. Various

genetic, immunological and micro- and macro-environmental factors are believed to be involved in the development of BD. The HLA-B*51 allele and variants in IL-10, TNF-α, TGF-β and at the IL-23–IL-12RB2 loci are the genetic factors most closely associated with BD. The variations in the association between various polymorphisms discussed and BD in different ethnicity/populations may reflect the heterogeneity in the genetic susceptibility to this disorder. Since the clear pathogenesis of BD remains to be elucidated, it is highly suggestive that multiple host genetic factors are involved in the development of BD. Therefore, further genetic studies on BD patients of different ethnicity and genes associated with immunity are expected to elucidate BD pathogenesis and also to contribute to the development of more targeted therapies and biomarkers.

Acknowledgements

Authors wish to thank MSD administration for facilities and support.

Conflict of interest

No conflicts of interests.

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